Clinical Validity of Insulin Bolus Calculators

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FDA Public Workshop: Regulatory Science Considerations for Software Used in Diabetes Management

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Joslin Diabetes Center

Harvard Medical School

Presenter Disclosure Information

Abbott Diabetes Care
Glooko
Tidepool

Topics for Discussion

QUESTION 1: How can patients and providers be confident that the insulin bolus values obtained from the calculators are accurate and appropriate for their use?

QUESTION 2: What information do patients and providers need about how a particular calculator works so that they may appropriately use the calculator for diabetes management?

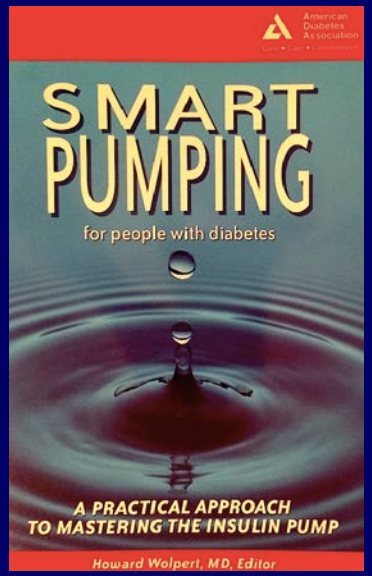
QUESTION 3: How can FDA foster both innovation and safety of insulin dose calculators intended for use by healthcare practitioners?

QUESTION 4: How can FDA foster both innovation and safety of insulin dose calculators intended for use by patients?

Topics for Discussion

QUESTION 1: How can patients and providers be confident that the insulin bolus values obtained from the calculators are accurate and appropriate for their use?

How is insulin often dosed in practice?



Book dedicated to……

Karl B. Smith, Jr. (1916 – 2006)

Diagnosed with diabetes summer 1922, aged 6

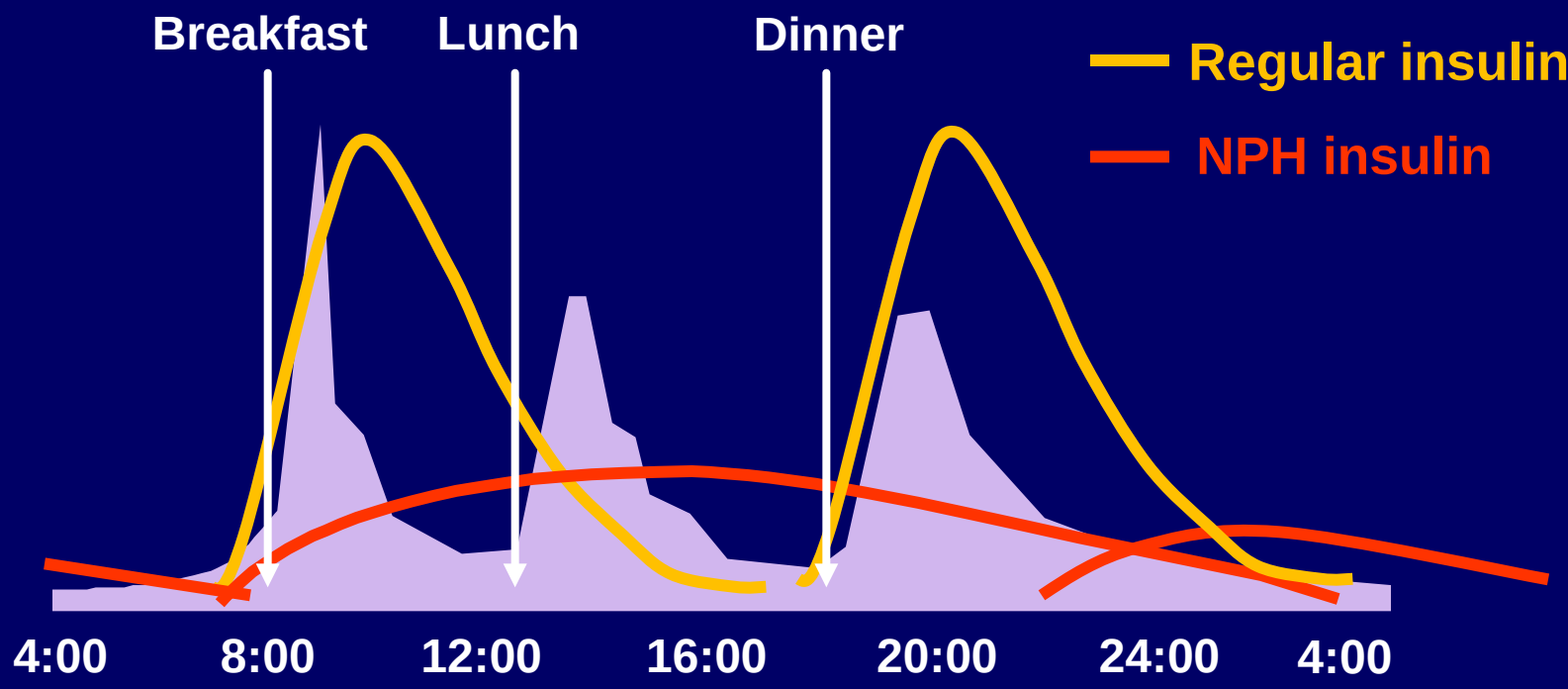
Died winter 2006, three weeks before 90th birthday: tennis in the morning, followed by lunch, failed to wake up from afternoon siesta

Personal experience informs what is best for individual patients
Patient is the ultimate decision-maker in day-to-day diabetes management
Clinician's role is not simply to prescribe insulin doses, but to guide the patient in making informed dosing and diabetes self-management decisions

Collaborative - instead of prescriptive - model of care required in diabetes has implications for how many patients can be expected to use bolus calculators

Standard Insulin Replacement Regimen in T1D

Early 1990's



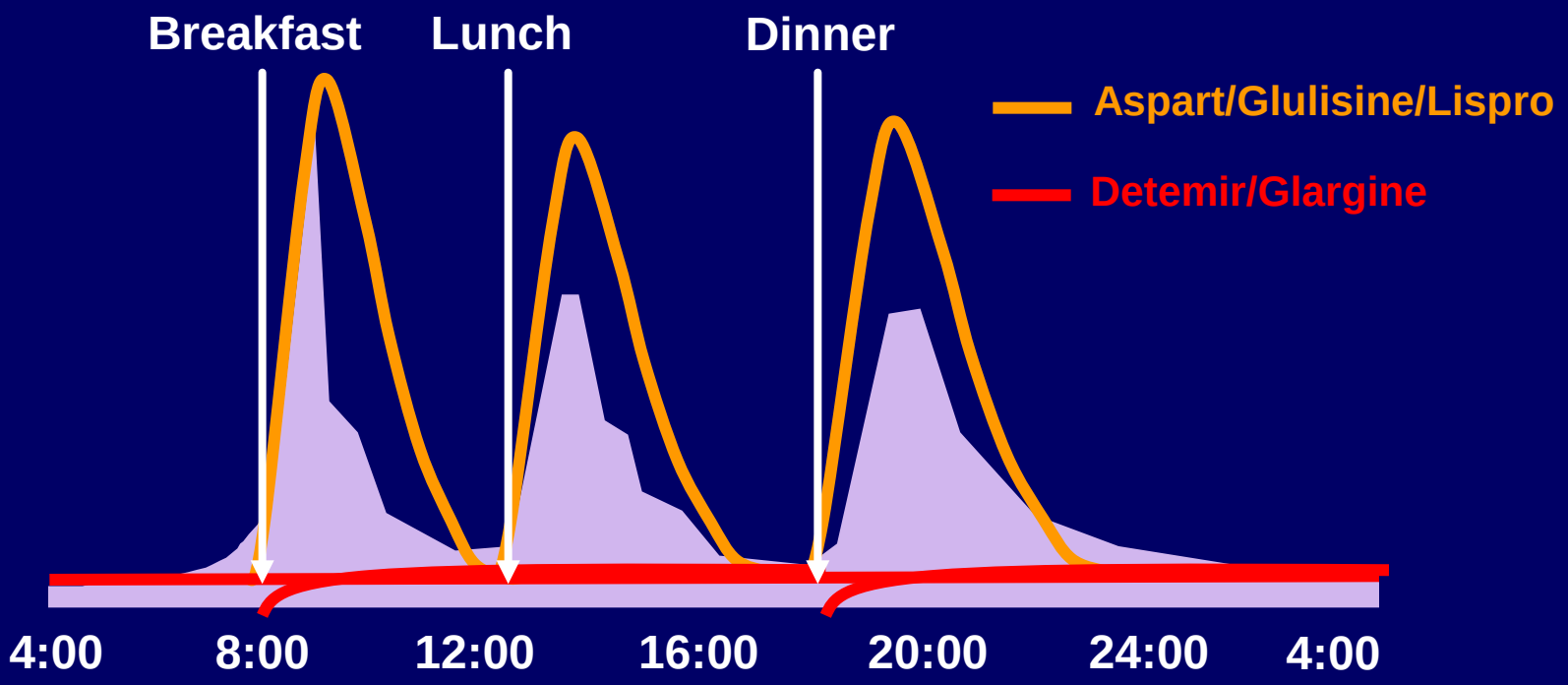
Constraints: Eating had to organized around the insulin profiles

Insulin dosing: Relatively fixed

Trade-off: Less flexibility in eating → often poorer adherence

Basal-Bolus/Flexible Insulin Therapy:

Past 2 decades



Milestones in the evolution of intensive insulin therapy:

- **1993:** DCCT
- **1995:** Introduction of 1st analog insulin (Lispro)
- **2003:** Introduction of 1st pump with bolus calculator (Deltec Cozmo)

The Current Approach: Food Insulin Dose Calculation

Carbohydrate quantity	X	Insulin-to-Carb ratio	=	Insulin dose

This dosing formula - which is incorporated in current insulin bolus calculators - has never been scientifically validated

Does this approach work in practice?

Yes….but, not as well as is supposed

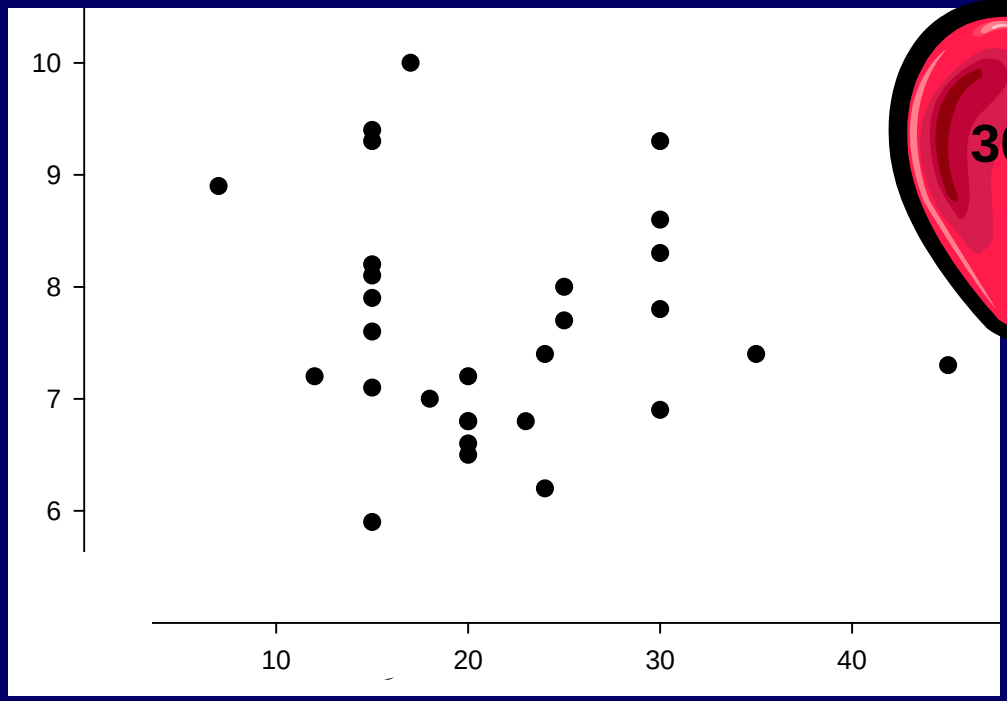
Limitations and Assumptions…..

Carbohydrate quantity	X	Insulin-to-Carb ratio	=	Insulin dose

Is accuracy in carb counting a realistic goal for most patients?

Carbohydrate counting skills in adult pump patients at Joslin

HbA1c



Patient estimated quantity (grams)

Limitations and Assumptions…..

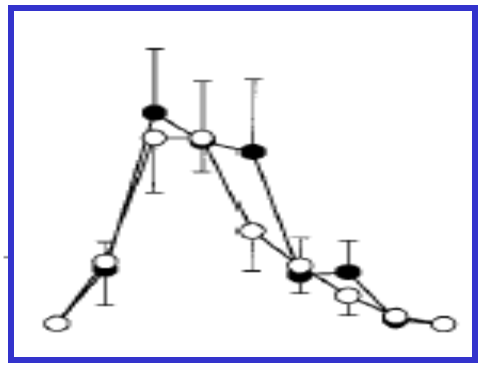
Carbohydrate quantity X **Insulin-to-Carb ratio** = **Insulin dose**

Is accuracy in carb counting a realistic goal for most patients?

Assumes that carbs are the only dietary ingredient that affects insulin requirements. Is there any scientific validity to carb-based insulin dosing?

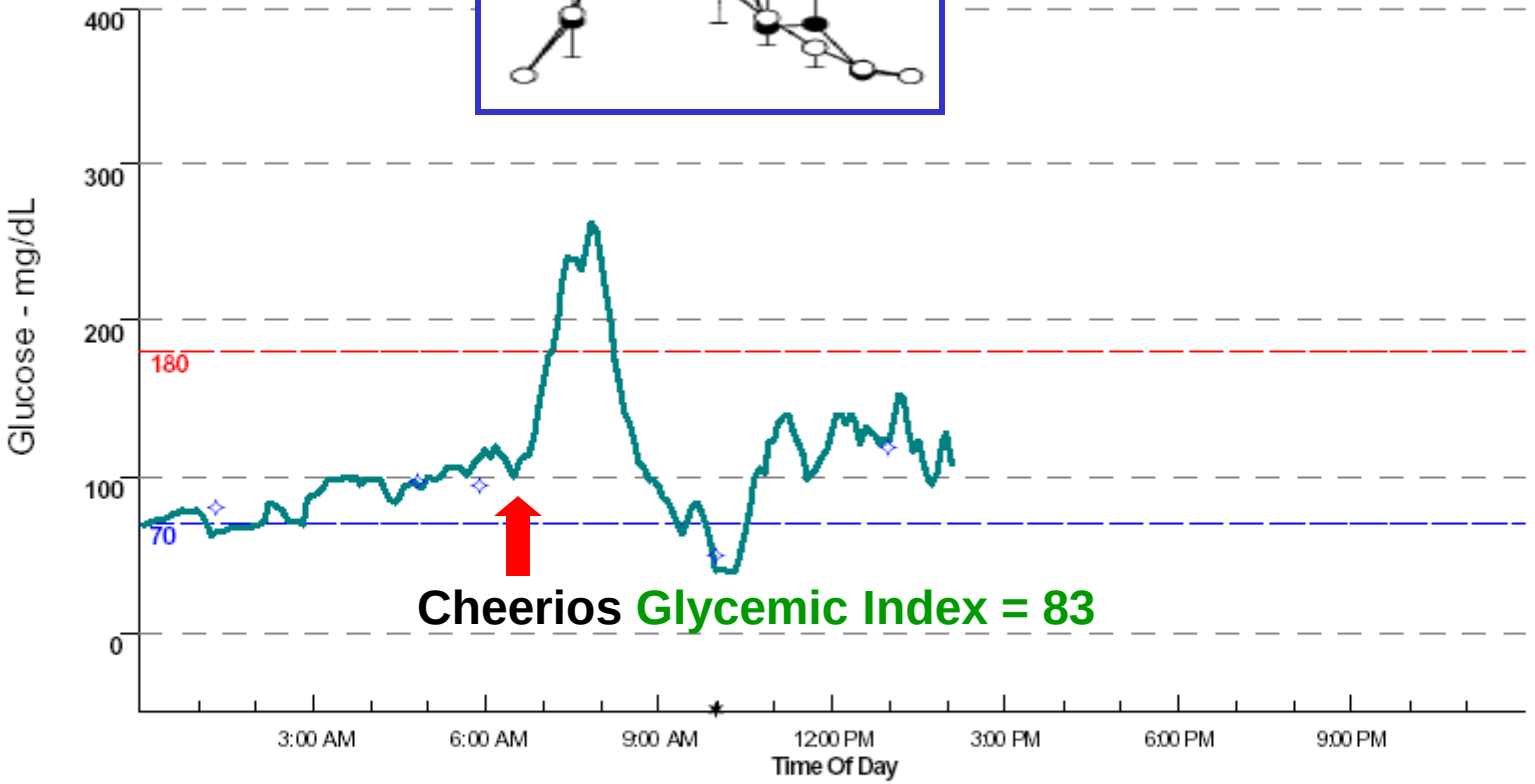
Assumes that getting the insulin dose correct is all that matters. To achieve optimal postprandial glucose control insulin action needs to match carb absorption

Insulin Pharmacodynamics



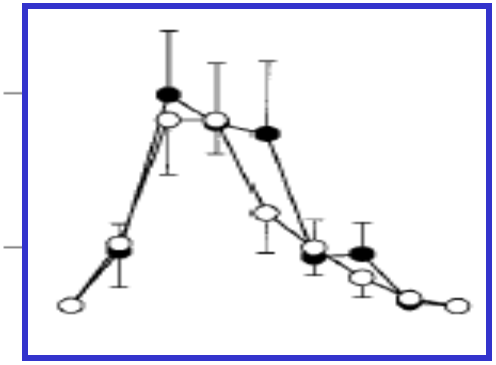
● Aspart

○ Lispro



Cheerios Glycemic Index = 83

Insulin Pharmacodynamics



● Aspart

○ Lispro

Glucose - mg/dL

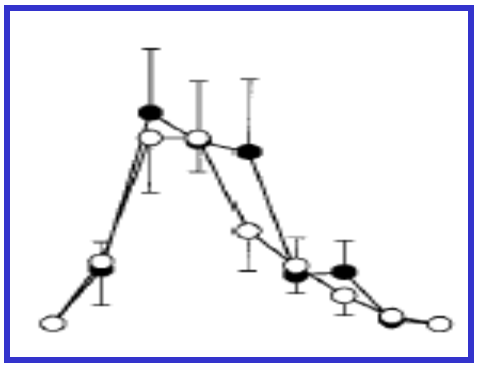
400
300
200
180
100
70
0

Oatmeal Glycemic Index = 49

To optimize postprandial glucose control, sometimes need to change food choices

Highlights the limitations of focusing on “accuracy” of bolus calculator settings alone as a key therapeutic endpoint in intensive diabetes management

Insulin Pharmacodynamics



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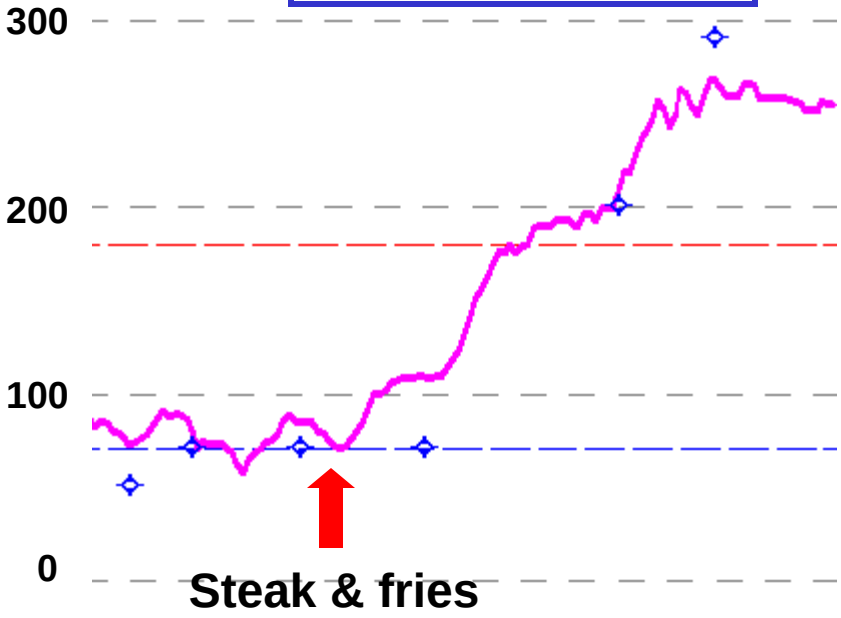
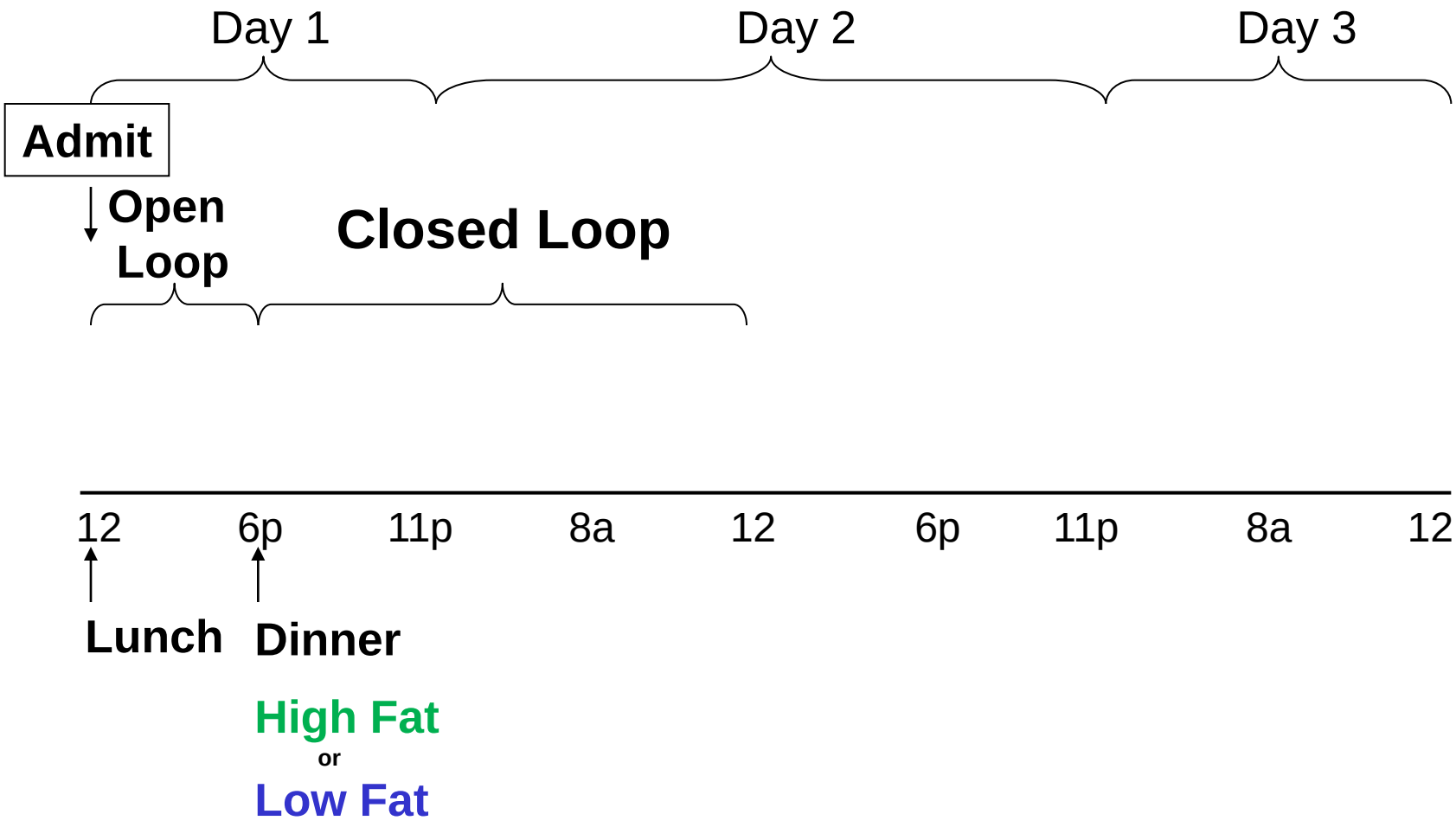


Free fatty acids induce insulin resistance

Does dietary fat increase insulin requirements?

Roden et al, *J Clin Invest* 1996; 97:2859
Belfort et al, *Diabetes* 2005; 54:1640
Boden et al, *Diabetes* 2001; 50:1612
Frias et al, *Diabetes* 2001; 50:1344

Closed Loop Protocol in CRC



Wolpert et al, *Diabetes Care* 2013; 36:810

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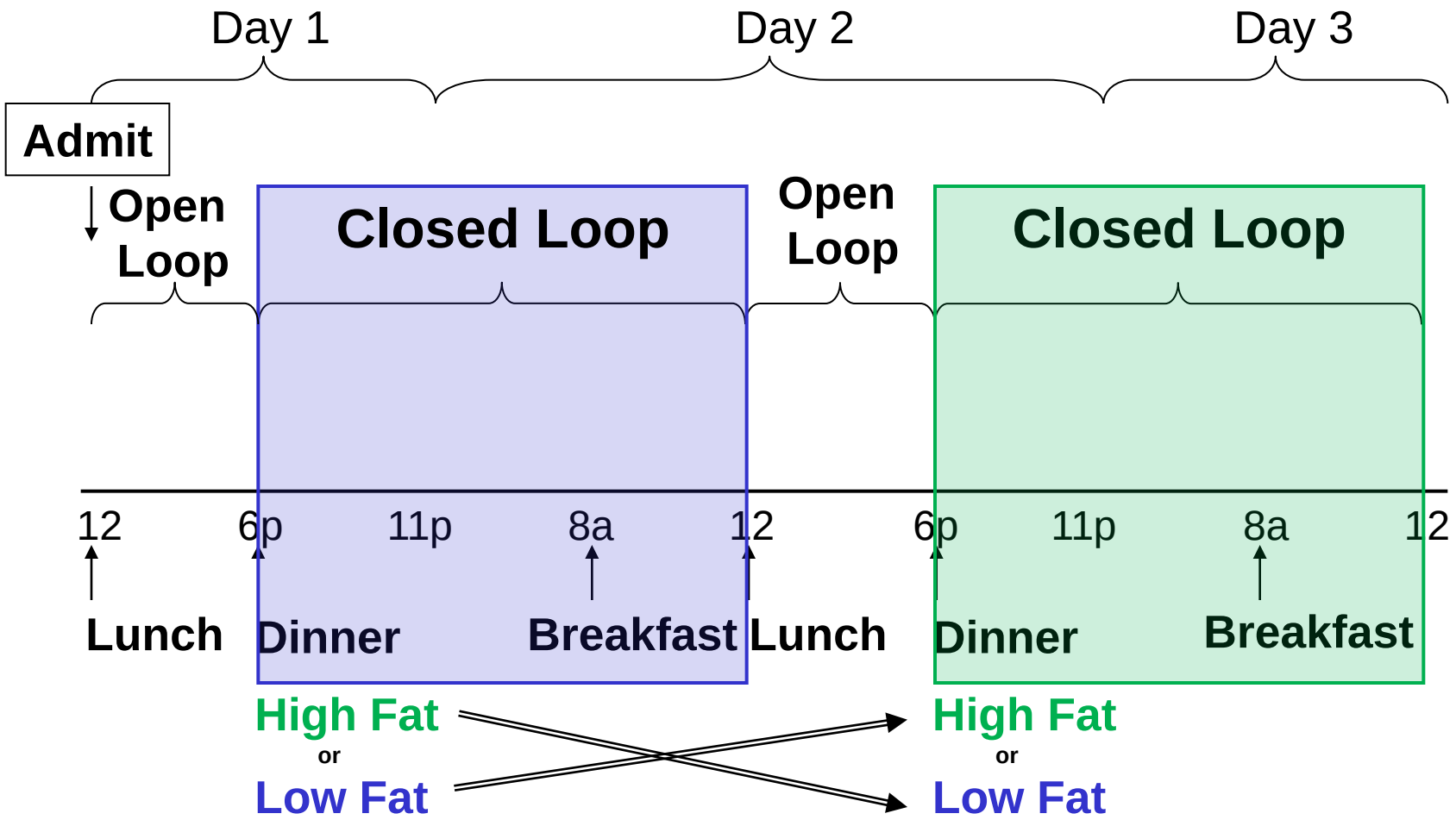
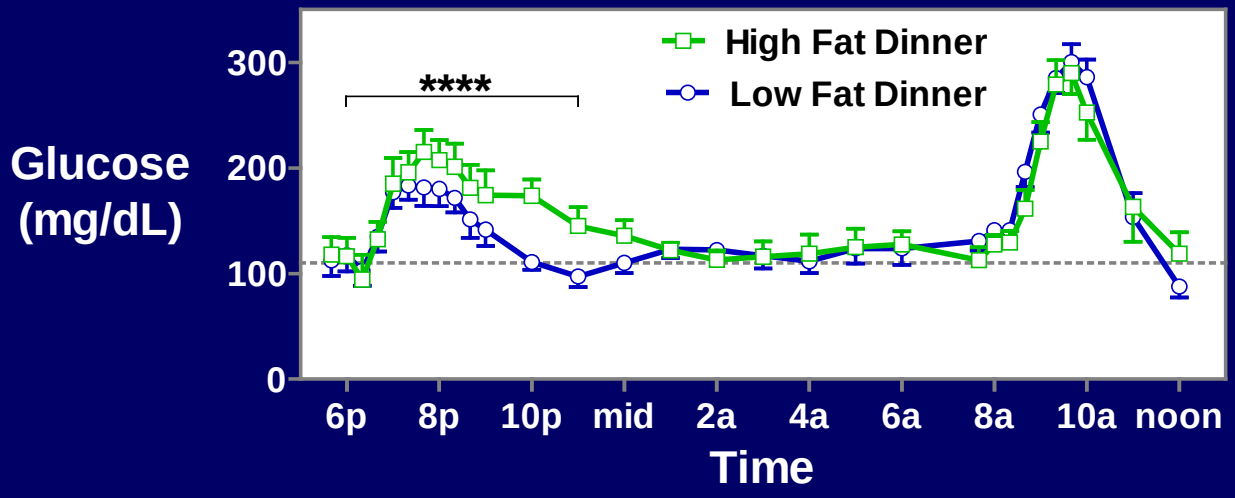


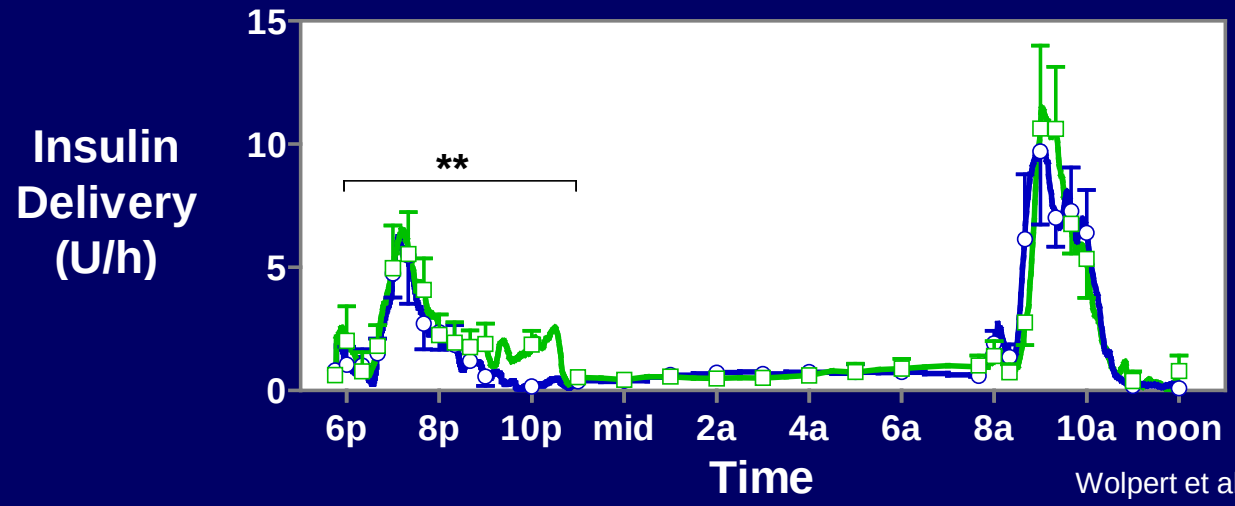
Wolpert et al, *Diabetes Care* 2013; 36:810

Dietary Fat Acutely Increases Glucose Concentrations and Insulin Requirements in Patients With Type 1 Diabetes

Implications for carbohydrate-based bolus dose calculation and intensive diabetes management



**** $p < 0.0001$



** $p < 0.01$

Wolpert et al, *Diabetes Care* 2013; 36:810

Carbohydrate quantity	X	Insulin-to-Carb ratio	=	Insulin dose

The current approach to food insulin dose calculation – incorporated into current bolus calculators – is not scientifically valid

In practice, to achieve optimal glycemic control patients need to adjust the insulin dose based on other factors, including activity, dietary fat, alcohol, etc

Carbohydrate quantity	X	Insulin-to-Carb ratio	=	Insulin dose

QUESTION 1: How can patients and providers be confident that the insulin bolus values obtained from the calculators are accurate and appropriate for their use?

All bolus dose recommendations – whether generated by a bolus calculator or derived from a paper-based algorithm – are inherently inaccurate since do not incorporate adjustments for other factors affecting prandial insulin requirements

In practice, these bolus recommendations are starting point in insulin dosing decisions. Based on experience, patients learn whether dose is appropriate for their use

Use Cases for Insulin Bolus Calculators

All time | Most time | Some time | Rarely | None

- Newly-diagnosed T1D
- T1D during intensification phase (not yet confident in self-adjustment)
- Physiologically changing insulin requirements e.g. childhood/adolescence, pregnancy
- Initial dose titration e.g introduction of basal insulin in T2D
- Hospital-based protocols
- Limited numeracy
- Impaired cognition
- Low self-management confidence

- T1D with improving self-mastery of DM management

- T1D: Maintenance phase
- Independently minded
- Pre-contemplative/ Disengaged

QUESTION 2: What information do patients and providers need about how a particular calculator works so that they may appropriately use the calculator for diabetes management?

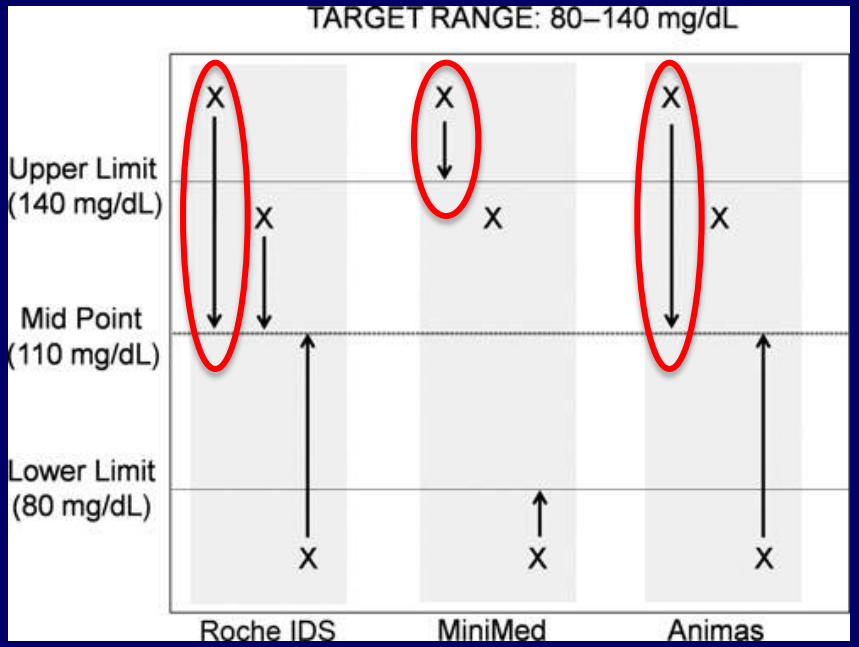
CORRECTION INSULIN BOLUS CALCULATION:

$$\frac{\text{Current glucose} - \text{Target glucose}}{\text{Sensitivity factor}} = \text{Correction dose} - \text{Insulin on board} = \text{Recommended Insulin dose}$$

Effect of Different Target Glucose Goals in Bolus Calculators on Correction Dose

$$\frac{\text{Current glucose} - \text{Target glucose}}{\text{Sensitivity factor}} = \text{Correction dose} - \text{Insulin on board} = \text{Recommended Insulin dose}$$

- Animas & Roche bolus calculators use mid-point of programmed target range in dose calculation
- Medtronic MiniMed bolus calculator uses upper limit of programmed target range in dose calculation



Zisser et al, *DT&T* 2010; 12:955

Effect of Different Target Glucose Goals in Bolus Calculators on Correction Dose

Protocol: Under-bolused for meal, corrected 2 hours later using boluses recommended by pump dose calculator

Head-to-head comparison of Animas, Medtronic MiniMed and Roche

TABLE 3. MEAN PREMEAL AND 2-H AND 6-H POSTPRANDIAL BLOOD GLUCOSE FOR TEST MEALS WITH 2-H BLOOD GLUCOSE >140 MG/DL THAT RECEIVED A BOLUS RECOMMENDATION

		Blood glucose (mg/dL)			
Device	*Number of meals*	*Preprandial*	*2-h postprandial*	*6-h postprandial*	*Bolus recommendation at 2 h*
Roche IDS	45	110.8 ± 31.4	231.6 ± 37.8	120.8 ± 34.7	1.45 ± 0.92
Animas	45	108.3 ± 31.2	226.4 ± 38.2	126.7 ± 42.4	1.26 ± 0.96
MiniMed	22	127.0 ± 39.1	260.3 ± 32.3	154.6 ± 37.0	1.04 ± 0.77

Data are mean ± SD values.

Hypo Events
2
2
0

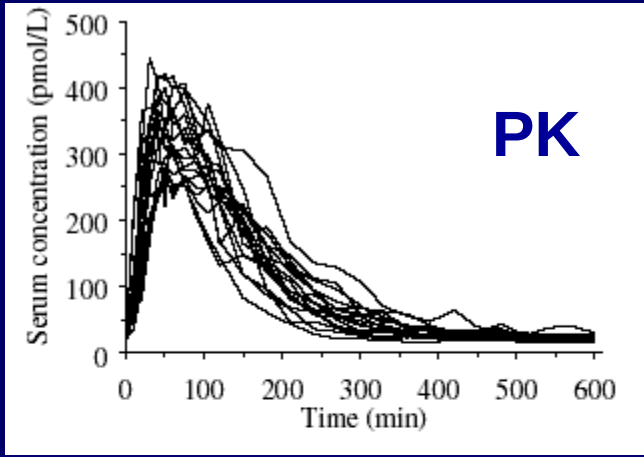
Zisser et al, *DT&T* 2010; 12:955

Considerations in the Settings for Insulin-on-Board Function in Bolus Calculators

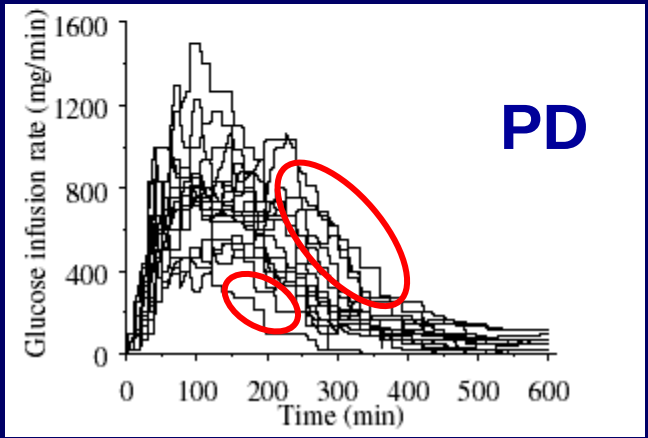
$$\frac{\text{Current glucose} - \text{Target glucose}}{\text{Sensitivity factor}} = \text{Correction dose} - \text{Insulin on board} = \text{Recommended Insulin dose}$$

Considerations in Calculating IOB

1. Insulin duration of action



Pharmacokinetic data (package inserts) is misleading about insulin action profile



Aspart (NovoLog) insulin

Marked inter- and intra-individual variability

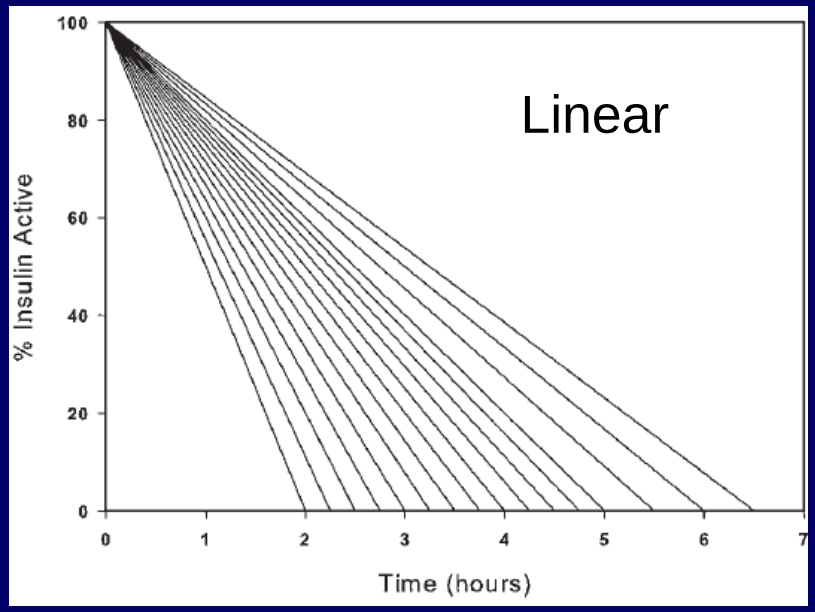
Other factors include:

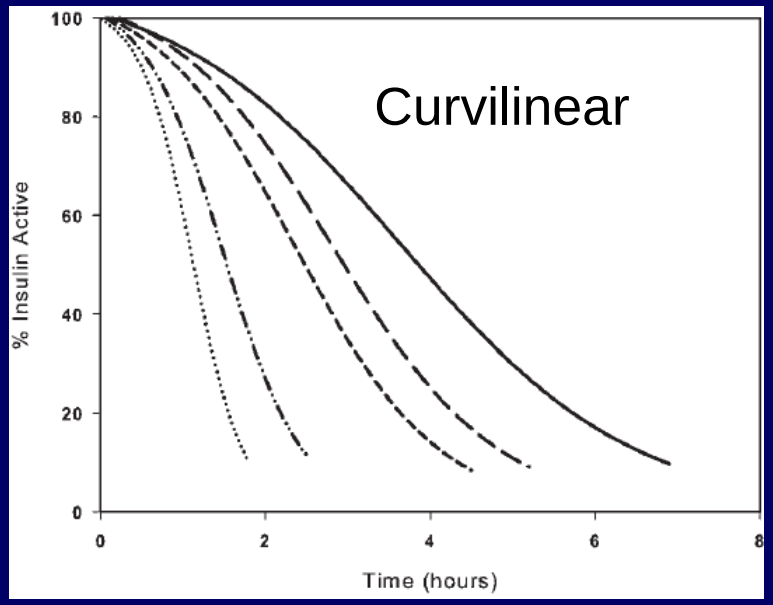
- Insulin dose
- Temperature
- Exercise
- SC fat thickness

Østerberg et al, *J Pharmacokinetics & Pharmacodynamics* 2003; 30:221

Considerations in Calculating IOB

2. Pump differences in insulin action curve





Driven by IP considerations and competitive marketing, little practical relevance

Zisser et al, *DT&T* 2008; 10:441

Practical Considerations in Setting Insulin Duration of Action

Primary consideration in selecting insulin duration of action is risk for hypoglycemia from dose stacking

If priority is avoidance of hypoglycemia (e.g. hx of severe hypoglycemia, hypoglycemia unawareness) set duration longer

- Reduces risk for stacking and hypoglycemia
- But may overcompensate for IOB, leading to under-dosing and failure to adequately correct

What Insulin Bolus Should the IOB Calculation Consider ?

When calculating correction bolus:

Approach #1: Subtract out IOB from previous correction bolus only, or

Approach #2: Subtract out IOB from previous correction + carbohydrate bolus

Depends on type of carbohydrate load consumed:

Approach #1 assumes carbohydrate-on-board at time correction dose is taken i.e. low glycemic index meal

Approach #2 assumes NO carbohydrate-on-board at time correction dose is taken i.e. high glycemic index meal

In practice: #2 will lead to more aggressive reduction in correction dose, protecting against hypoglycemia

QUESTION 2: What information do patients and providers need about how a particular calculator works so that they may appropriately use the calculator for diabetes management?

1. While patients need to know the key elements in dose calculation, not realistic to expect most patients or clinicians to understand complexities and nuances of IOB calculations
2. In practice, important to know whether particular IOB settings are biased to aggressive vs cautious insulin delivery

QUESTION 2: What information do patients and providers need about how a particular calculator works so that they may appropriately use the calculator for diabetes management?

3. Impossible to perform scientifically-valid studies to evaluate bolus calculators that would be generalizable to real-world use
   Experimental challenges include:
   - Appropriate attention control group
   - Difficulty in isolating benefit of bolus calculator from other variables (such as carb counting skills) that are determinants of success in using the technology
   - Appropriate characterization of study population (likely benefit from/need for bolus calculator depend on diabetes self-management mastery)
   - Inherent bias of algorithms related to food choices

QUESTION 3: How can FDA foster both innovation and safety of insulin dose calculators intended for use by healthcare practitioners?

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Break down the questions:

How can FDA foster both innovation and safety of bolus calculators?

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QUESTION 4: How can FDA foster both innovation and safety of insulin dose calculators intended for use by patients?

Break down the questions:

How can FDA foster both innovation and safety of bolus calculators?

How does intended use of bolus calculators by healthcare practitioners and patients differ?

How Does Intended Use of Bolus Calculators by Health Care Practitioners and Patients Differ?

- Healthcare practitioners and patients use bolus calculators in different environments

  > challenges and priorities in diabetes management in medical facilities are different to home/outpatient setting
- In outpatient diabetes management precedence is on flexibility in dosing with deviation from prescribed boluses to account for other factors (such as activity, alcohol, etc), whereas in the hospital the focus is on close adherence to prescribed medication dosing protocols
- In ICU: fewer confounding factors affecting glucose (food intake, exercise) + faster insulin action time (iv)

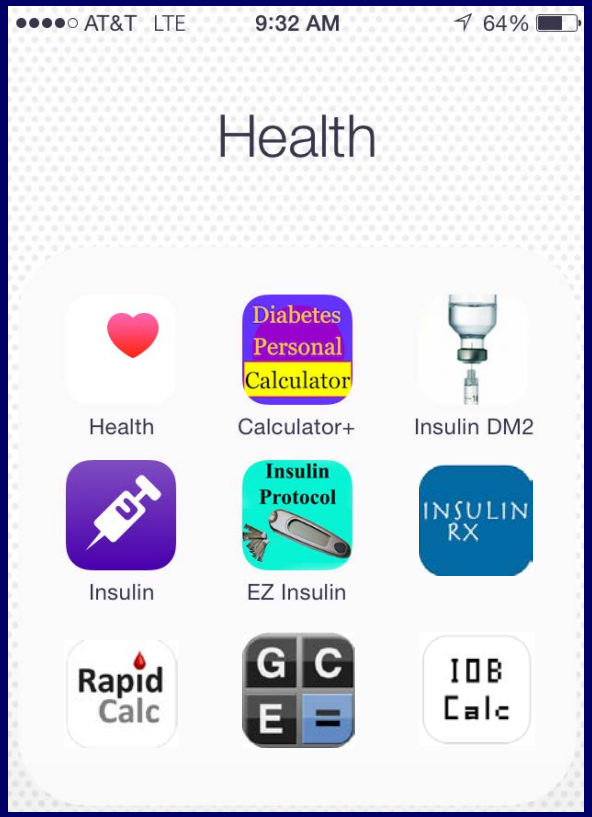
  > tight glycemic control easier to accomplish with less need for deviation from prescribed protocols
- Scientific validity of dosing algorithms used by health care practitioners in ICU can be evaluated much more readily than that of insulin bolus calculators used by patients in home environment

  These differences need to be factored into regulatory requirements

Bolus Calculator Tools: Today

Regulated Medical Devices

Smartphone Apps



Innovation, no regulation

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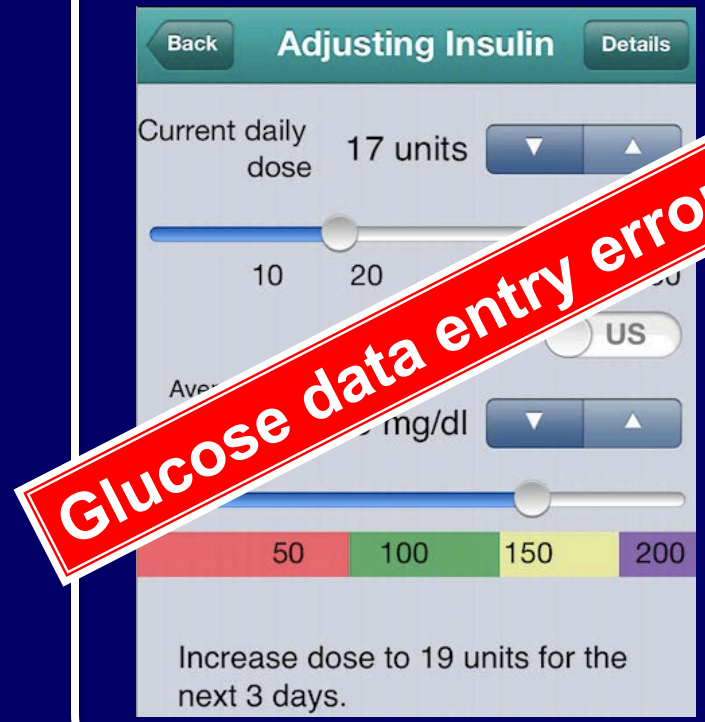

Glucose data entry errors

Innovation, no regulation

Bolus Calculator Tools: Today

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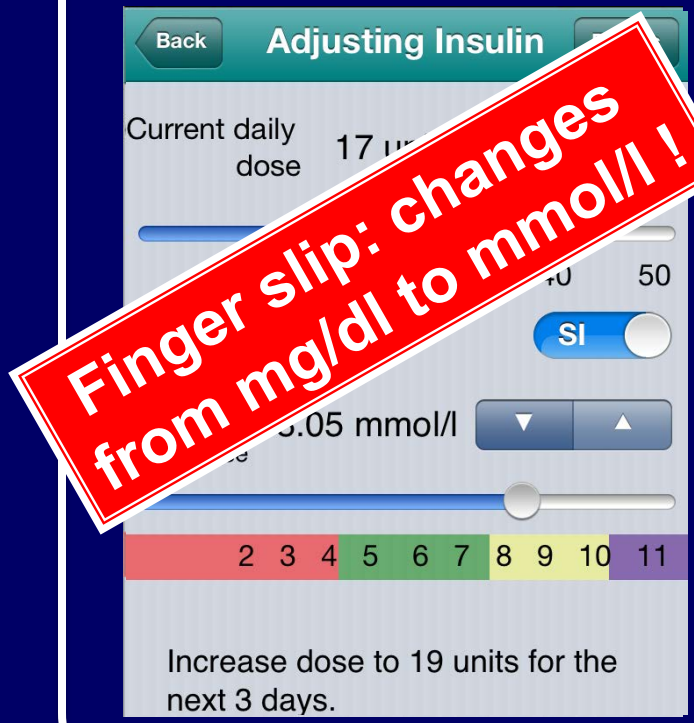


Finger slip: changes from mg/dl to mmol/l !

Innovation, no regulation

Bolus Calculator Tools: Tomorrow

Balancing Innovation and Safety

Regulated Medical Devices

Regulated Diabetes Data Management and Decision Support Platforms

Diabetes Management Apps: Software Validated

glooko

livongo health

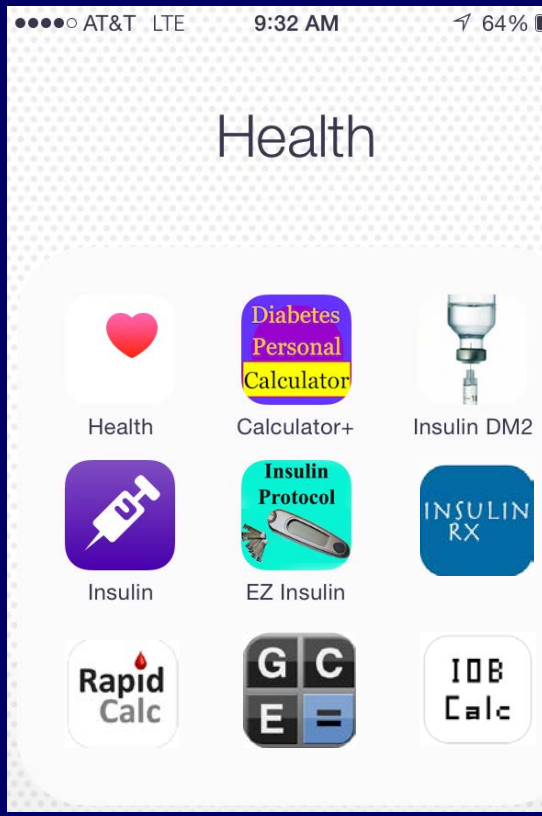
TELCARE™

TIDEPOOL

Data Inputs

Glucose
Insulin
Activity
Food

Smartphone Apps



Regulatory Science Considerations for Software Used in Diabetes Management

Concluding Comment

Different risk mitigation approaches and regulatory pathways are required for:

1) Software that operationalizes paper-based insulin dosing instructions, including algorithms, prescribed by HCPs in routine diabetes management

versus

2) Software incorporating more sophisticated insulin delivery algorithms that automatically optimize insulin doses without HCP verification (such as AP)

Case 2) requires full clinical trials since HCP is not in the loop, whereas for Case 1) strict adherence of the software company to quality control, including extensive testing and usability studies with patients and HCPs, would be adequate

Thank you